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Saliva as a Diagnostic Fluid for Periodontal Diseases: A Literature Review

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KEYWORDS

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ABSTRACT:

Most of the periodontal disease diagnostics are based upon traditional clinical methods of assessment like bleeding upon probing, clinical attachment level and probable pocket depth. These methods monitor disease history rather than appraising the disease activity or predicting future risk of periodontal breakdown. The field of salivary diagnostics is a promising target for risk determination of periodontal diseases. Saliva is a hypotonic biofluid containing a variety of hormones, enzymes, cytokines, bacteria, and their by-products. Salivary analytes may reveal existing disease severity as well as activity and may help in the subject level risk assessment of periodontal disease. The use of salivary diagnostics as a reliable means for risk assessment, preliminary diagnosis, establishing prognosis, and post-therapy status monitoring shows significant promise.

1. Introduction

Saliva is a biofluid with contribution from crevicular fluid, serum, oral cavity and reflects a whole mouth analysis sample. Salivary components comprise proteins of host as well as bacterial origin (immunoglobulins, cytokines & enzymes), genetic markers such as host-derived DNA and mRNA, ions, volatile compounds, bacteria and bacterial products, and steroid hormones. It represents the physiological condition and variations in various systems of the body. Its composition essentially reflects the full range of both healthy and disease-related states of the body.

Early diagnosis of disease is vital in prevention of difficulties and complications that could have a negative influence on patients' quality of life.

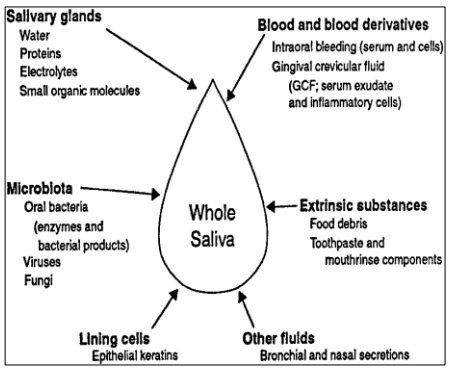

Fig. 1 Composition of Saliva (Mandel et al,1976, FDI Working Group10, Core, 1992)

Periodontal disease is time consuming and expensive to treat, may lead to tooth loss, masticatory and digestive problems if left untreated, and therefore its prevention, early detection and management can yield considerable healthcare benefits (Vahabi et al., 2020). Despite advances in understanding the etiopathogenesis of periodontal diseases, most of the destruction of periodontal structures diagnostics are grounded upon traditional clinical methods of assessment like bleeding upon probing, clinical attachment level and probable pocket depth. These methods monitor disease history rather than appraising the disease activity or predicting future risk of periodontal breakdown (Zhang et al., 2021). Salivary analytes may reveal existing disease severity as well as activity and may help in the subject level risk assessment of periodontal disease.

A new non-invasive diagnostic approach has been made possible by the revelation that the molecular profiles in saliva reflect disorders in the body. The advances in proteomics, genomics and microbial biomarkers and integration of nanotechnology with microfluidic engineering have led to the emergence of small and efficient point-of-care devices for prompt quantification of biomarkers in saliva. Disease-specific markers can prove to be valuable in risk determination, preliminary diagnosis, prognostic evaluation, and post-therapy status monitoring.

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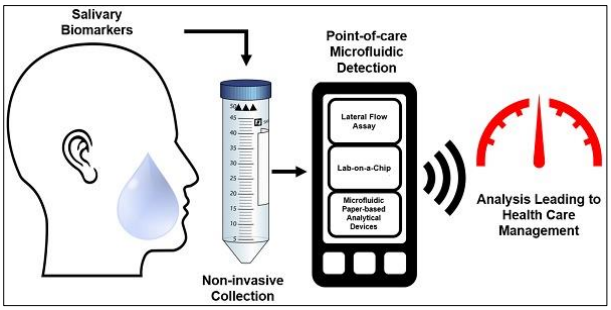

Fig 2. Point of Care Salivary Diagnostics

(Pittman TW. et al., 2023)

However specific biomarkers for early prediction of periodontal disease onset, distinct biological stages of the disease and progression of gingivitis to periodontitis are still under evaluation. Even though challenges remain, saliva is the most promising emerging diagnostic medium for periodontal disease.

2. Saliva as a diagnostic medium

Numerous compelling arguments authenticates the utility of saliva as a "real time" point-of-care fluid for diagnosis. (Kim et al., 2020, Kim et al., 2021, Ishii et al., 2022)

- Various proteins, peptides, inorganic and organic salts, blood electrolytes and contributes from mucosal transudates and gingival crevicular fluid are contained in saliva
- Collection is comfortable, non-invasive, and inexpensive
- It is readily available
- Easy and rapid collection
- No special equipment or expertise required
- Safer than blood collection for professionals
- Do not coagulate hence easier to handle and process for diagnostic procedures
- Easy storage and transportation
- Minimal risk of cross-contamination
- Whole mouth summary analysis

Either an unstimulated or a stimulated collection can provide whole saliva. By masticatory or gustatory stimulation, such as chewing on paraffin or putting citric acid on the patient's tongue, stimulated saliva collection is made possible (Ramenzoni et al., 2021). Unstimulated saliva collection happens when there is no stimulation (mechanical or masticatory) and is mostly influenced by the participants' degree of hydration.

Identification of markers specific to a disease, test sensitivity and specificity, and standardization of salivary sample collection and storage are concerns of using saliva for diagnostic purposes. With the greater understanding of the field of salivaomics supported with the arrival and development of novel, sophisticated and highly sensitive and sophisticated technologies like microarray and next generation sequencing (NGS), the problem of lesser quantity of salivary analytes may be taken care to a larger extent (Nisha et al., 2019). These characterises help make saliva an attractive diagnostic medium for examining the various biomarkers in patients of all age group, as well as systemically compromised and physically challenged and uncooperative patients.

3. Review of Literature

Alkimavičienė, E et al., 2023 conducted the study to see the utility of proanthocyanidins (PACNs) as a supplementary treatment in individuals with periodontal disease. Individuals who had with stage III -IV periodontitis were randomly assigned to either minimally invasive nonsurgical therapy or MINST along with PACNs (MINST + PACNs). Before and after treatment relevant clinical periodontal markers were assessed. Markers of immunological processes, markers, matrix metalloproteinase-3 and tissue inhibitor of MMP1 salivary concentrations were measured in the beginning of the study and 8 weeks later. In mild periodontal pockets, PACNs paired with non-surgical therapy led to a statistically significant reduction in PPD and CAL gain of average 0.5 mm when competed with the non-surgical treatment alone. However, bleeding on probing and plaque index values did not reveal any significant improvement in MINST+ PACN group. After 8 weeks of application, MMP-3 levels in saliva decreased substantially. The addition of PACNs to MINST caused improved clinical findings for moderate pockets. MMP-3 concentration in saliva which reflects healthy periodontium was raised by using PACNs in addition to MINST alone.

Görgülü, N. G., & Doğan, B., 2022 conducted a study with the purpose of comparing the levels of total macrophage-activating factor, macrophage colony-stimulating factor, macrophage inflammatory protein, matrix metalloproteinase-8, as well as interleukin -34 in

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blood serum and saliva of subjects with healthy periodontium, periodontitis Stage III Grade B and Stage III Grade C. Clinical parameters were documented, and samples were accumulated from all individuals as the study ensued. Parameters to assess the periodontal status were revaluated in periodontitis groups, and samples were taken at 1 and then at 3 months after treatment. ELISA was used to assess the levels of biomarkers. After NSPT, all periodontal metrics improved in periodontitis groups. Salivary MMP-8 and MAF levels showed greater levels in individuals with periodontitis as equated with control group at baseline and dramatically lowered following NSPT to healthy levels or below. Both periodontitis groups showed the strongest diagnostic ability for salivary MMP-8. Furthermore, after controlling for confounding factors salivary MMP-8 and macrophage activating factor levels were corelated with the stage and grade of periodontitis.

Ishii, K. et al, 2022 sought to examine and find a salivary biomarker capable of predicting the inflammatory condition of periodontal disease. The study included 36 patients whose saliva (unstimulated) was collected and analysed using an instrument namely SillHa, that detects acidity, buffer capacity, bacterial count, leukocyte esterase, protein as well as ammonia in salivary samples. Clinical examination was subsequently used to acquire periodontal parameters, and first periodontal treatment was administered. SillHa data were compared to the recorded periodontal measures at baseline, and three months later and eventually six months after re-examination. Between baseline and concluding investigation, as well as re-examination and final examination, a substantial difference in leukocyte esterase activity in the patients in the group with lower medium values was noticed. Furthermore Group 1 subjects had considerably lower bleeding on probing between baseline and final check-up. Individuals with higher medium value had a modest decrease in the activity of leukocyte esterase that was only substantial between baseline and closing evaluation, but no significant variations in BOP were seen. The outcomes propose that SillHa-measured salivary leukocyte esterase activity in might be a useful marker for monitoring the inflammation in periodontitis.

Kim HN, 2022 Post week sixth of NSPT (non-surgical periodontal treatment), the current findings sought to determine variations within clinical parameters and amounts of matrix metalloproteinases (MMPs) in saliva. 51 adults under the age of 20 were given a 6-week NSPT programme. Scaling, root planing, and expert toothbrushing were all included of the programme for both healthy and periodontal disease patients. During each of the three appointments, patients with periodontal disease had their teeth professionally brushed. Salivary samples were taken to establish the levels of MMP-9, -8, and -3, and gingival bleeding and periodontal pocket depth (PD) were documented at weeks 0, 3, & 6. Post-NSPT course, all recorded clinical parameters in the groups with periodontal disease demonstrated improvement. The subjects with periodontal disease had higher levels of MMP-3, -8, and -9 in saliva as compared to the healthy subjects. Individuals who had periodontitis also shown significant decrease in gingival bleeding along with PD during the 3rd week of the 6-week programme; however, no such reductions were observed by the 6th week. At week 3, it was discovered that the periodontal disease group had significantly reduced strengths of MMP-3, -8, and -9 in saliva than the control group. Thus, the current study demonstrated MMP-3's potential to be used as a marker for the periodontal disease detection.

Junior RL et al., 2021 in the study to assess the myeloid-related measures of biomarkers in saliva in connection to periodontitis, their prospective for screening, and the influence of therapy on these markers in patients with periodontitis included individuals with healthy periodontal tissues, gingivitis, and periodontitis. Patients with periodontitis received non-invasive treatment followed by check-ups after three and six months. Saliva samples from the periodontitis patients were taken at baseline, as well as 1, 3, and 6 months after treatment. Immunoassays were used to measure the levels of hepatocyte growth factor (HGF), interleukin-34 (IL-34), matrix metalloproteinase-8 (MMP-8), interleukin one (IL-1), colony-stimulating factor 1 (CSF-1), S100A8/A9, and S100A12. While IL-34 was reduced in periodontitis patients, the other assessed parameters were suggestively greater in saliva from periodontitis as well as gingivitis patients in comparison to individuals who were healthy. While IL-1 and MMP-8 reduced one month after therapy, IL-34 dramatically rose three months after therapy. Additionally, individuals with periodontitis were grouped into groups based on their S100A8/A9 levels, with those with greater levels having deep value pockets,

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elevated incidences of bleeding, and higher S100A12 levels. Thus, conclusion that can be made is periodontitis affects the amount of myeloid related markers in saliva along with periodontal therapy can partially modify this effect. Saliva S100A8/A9 measurements may be used to classify different types of periodontitis patients.

Kim HD et al., 2021 compared the correlation and assessing capacities of S100A8 and S100A9 in blood, GCF as well as saliva to determine prevalence of periodontitis. Researchers enrolled 149 community-dwelling Korean individuals, 50 of whom had no or early periodontitis and 99 had advanced periodontitis. Stages II to IV of the revised periodontitis classification proposed in 2018 were used to classify established periodontitis. This was done incorporating clinical attachment level and a panoramic radiograph. S100A8 and S100A9 were analysed incorporating an ELISA test kit. Between S100A8 and S100A9, S100A8 in saliva was substantially elevated in patients with established periodontitis in comparison to S100A8 in blood and GCF. S100A8 and S100A9 in GCF, on the other hand, were higher in patients with no or initial periodontitis. Blood S100A8 and salivary S100A8 had a progressive association. Hence, the investigation concluded- salivary S100A8 may be a valuable screening tool for established periodontitis and a potential diagnostic marker for the condition.

Ramenzoni LL et al., 2021 study's objective was to assess the efficacy of diagnostic salivary assays for determining periodontal health. Twenty individuals with III stage grade B generalised periodontitis along with twenty individuals in good periodontal health had their whole saliva analysed for calcium, alkaline phosphatase, lactoferrin, buffer capacity, osmolarity, density, phosphate, pH, salivary flow rate, and dynamic viscosity. The salivary indicators of inflammation, clinical periodontal parameters, and bacterial pathogens were all assessed using a semiquantitative urine strip test. Lactoferrin, haemoglobin, and leukocyte concentrations were found to be suggestively elevated in periodontitis patients stimulated as well as unstimulated saliva compared to healthy participants, while amount of alkaline phosphatase were higher within the latter group. Hence the examination inferred that test-strip-based examination of periodontal biomarkers may be regarded a quick and simple method for identifying patients with periodontitis from those who are healthy. Strip tests that measure the rise in lactoferrin, haemoglobin, and leucocytes may offer a non-invasive way to diagnose periodontitis.

Chen, Y. et al., 2021 The purpose of this cross-sectional analysis conducted on 111 orthodontic patients was to examine the correlation between pro-inflammatory cytokine levels in saliva and gingival health and oral microbial burdens. The periodontal indices were used for clinical examinations to determine gingival health status. Salivary microbiological tests were performed to determine the entire anaerobic as well as aerobic bacteria count, lactobacilli, and streptococci count. Interleukin-1beta and macrophage migration inhibitory factor ELISA tests were used to investigate saliva immunology. Salivary IL-1beta levels were shown to have moderate positive connections all the microbes studied, and weak positive correlations with total salivary bacterial (aerobes & anaerobes) counts. A link was discovered between salivary levels of Interleukin-1beta and the bleeding index. Thus, the study concluded, IL-1 beta concentrations in saliva correlate with bacterial burden in the oral cavity in orthodontic patient however the relationship between oral microbiota and inflammatory cytokines warrants additional investigation.

Tar, I. et al., 2021 in their research aimed to evaluate and correlate periodontal status of rheumatoid arthritis patients with the citrullinated protein levels in saliva as well the salivary and serum levels of the protein indicators were related to periodontal health and temporomandibular joint involvement. The research included twenty-three RA patients and seventeen healthy controls. Saliva and blood samples were gathered. TMJ disorders were explained and indices for caries and periodontal disease were recorded, and staging were recorded plus measured levels were compared within and between groups. TMJ issues were much more common in the RA group than in the controls. Patients with RA exhibited lower periodontal health because they had more gingivitis and had considerably more bleeding on probin and higher gingival index (GI) scores. The salivary citrullinated protein didn’t show substantial difference between RA patients and healthy controls. Salivary anti-CCP levels in RA were favourably linked with PD stage. Control participants had healthier periodontium than RA patients.

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Rabelo, M. S.et al., 2021 The purpose of this trial was to examine the short-term effects of etiotropic periodontal therapy on saliva, serum and crevicular fluid inflammatory marker concentrations in generalized periodontitis participants with and without hyperglycaemia. 60 participants were separated into 4equal-sized units: normoglycemic patients suffering from GP pre-diabetics with GP, type 2 diabetics who has generalised periodontitis, and healthy controls. The samples from saliva GCF as well as serum, were collected at start and then a month after scaling and root paling, and the amount of various interleukins, interferon gamma, granulocyte macrophage colony-stimulating factor, and TNF-alpha were determined using a multiplex assay. Periodontal measurements were done. It was seen that SRP led to improvement of all clinical parameters. Also, there was a significant reduction in markers of inflammation locally in GCF and saliva especially in that of interleukin 1 beta and interferon gamma but the decrease of the markers in sedum was non-significant.

Joseph, B et al., 2020 study's goal was to determine the concentrations and analytical precision of salivary deoxypyridinoline-containing degradation fragment of type I collagen's C-terminal telopeptide region (CTX), osteocalcin and osteonectin, in smokers with alveolar bone loss. The analysis comprised ninety systemically healthy adults divided into 3 groups -healthy, periodontitis and non-smokers and periodontitis in current smokers. The results revealed a weak to moderate positive connection between assessed markers and probing pocket depth and alveolar bone loss.

Ucan Yarkac, F. et al., 2020 conduced a randomised controlled clinical trial to see if nonsurgical mechanical periodontal treatment affected the severity and inflammation in psoriasis patients. The study included ninety-two periodontitis patients with psoriasis vulgaris who had periodontal disease and were divided by random method into 2 groups of immediate and delayed periodontal therapy. Periodontal clinical measurements, Psoriasis Area, and Severity Index (PASI) scores, salivary levels of IL 6, IL 2, plus secretory immunoglobulin A levels were assessed in both groups at baseline and on the eighth week. Eight weeks after nonsurgical periodontal therapy or initial examination, a substantial reduction in levels of salivary interleukins, and PASI score was observed, whereas a significant increase in secretory immunoglobulin A levels was observed in the NSPT group. The findings of the investigation imply successful periodontal care decreases psoriasis in people with both disorders.

Varghese J et al., 2020 considered the 8-hydroxyguanosine (8-OHdG) levels in saliva in chronic periodontitis subjects in smokers and non-smokers following NSPT in a case-controlled clinical experiment. This study included 40 subjects with periodontitis and clinically healthy. Clinical periodontal markers were assessed at the outset. Samples of saliva were obtained before and subsequently after NSPT to determine the 8-OHdG amounts using ELISA. SRP were performed on participants with chronic periodontitis and smokers (CPs) as well as non-smoking subjects with periodontitis (CPns). Only oral hygiene instruction was done on clinically healthy participants. The salivary collection and qualification were repeated, and the clinical parameter were re-recorded three months later. Both periodontitis groups had substantially higher clinical parameters values at baseline than controls. When compared to the other groups, the CPs group had substantially higher baseline salivary levels of 8-OHdG. The clinical markers in the group with chronic periodontitis demonstrated improvement at the third month recall, except for 8-OHdG levels, which remained higher in the CP smoking group compared to the CP non-smoker group. This data indicates a persistent destructive state in smokers, and salivary 8-OHdG levels may be recognised as a biomarker for oxidation for assessing deterioration of health of the periodontium.

Zhang Y et al., 2021 to gauge the analytical performance of salivary MMP-8, interleukin (IL)-1, carboxyterminal telopeptide pyridinoline cross-linked type I collagen (ICTP), as well as Porphyromonas gingivalis (Pg), enrolled 80 participants for a cross-sectional study. The best diagnostic marker was found to be IL-1 as a single marker. Combining IL-1, ICTP, and Pg was the most efficient way to tell gingivitis and periodontitis patients apart from healthy people. Combining IL-1 and MMP-8 resulted in the superlative capacity to identify gingival disease from healthy subjects.

Kim HD et al., 2020 conducted a cross-sectional study was conducted over 137 subjects recruited from Seoul National Dental Hospital with the aim of examining the analytical competence and validity of (MMP)-9 within

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saliva using point-of-care (POC) kit. Unstimulated whole saliva was collected, and quantification of salivary MMP-9 was done using ELISA kit. Investigative competence of salivary MMP-9 test was found to be 0.82 and the study indicated that it could be a reasonable apparatus for inspecting of patients with periodontitis.

Kim HD et al., 2020 Through a clinical trial for non-surgical periodontitis treatment, study sought to assess the predictive value of salivary MMP-9 and S100A8 inside the larger family of S100 calcium-binding protein with the potential to bind with zinc). 50 healthy participants and 99 people with periodontitis totalled the 149 participants. 74 of the 99 patients receiving non-surgical therapy for periodontitis returned after three months. According to a new classification of periodontitis introduced in 2018, periodontitis was divided into stages II to IV. A kit ELISA was incorporated to measure the MMP-9 and S100A8 levels in saliva. Results reviled that periodontitis was related to salivary MMP-9 and S100A8 (p .05). An algorithm using the two measurements demonstrated high periodontitis diagnosis capability. MMP-9 and S100A8 from saliva both have the prospective to predict periodontitis outcomes, but S100A8 performed better.

Hartenbach FARR et al., 2020 conducted a comparative study, with the aid of mass spectrometry, which examined the salivary proteomic profile of people with chronic periodontitis (CP), subjects with healthy periodontium, (PH), correlating proteins with the clinical indicators of the condition. Ten PH and thirty CP patients stimulated entire saliva was collected, then combined into five healthy samples-control group and fifteen CP samples. Salivary SMR protein, acidic proline-rich phosphoprotein, histatin-1, fatty acid binding protein, thioredoxin, and cystatin-SA were found to be associated suggestively with signs of gingival inflammation and attachment loss, whereas a widespread variety of proteins in saliva were significantly down regulated in individuals with chronic periodontitis. In conclusion, just a few salivary proteins were linked to CP. These results might aid in the betterment of periodontal diagnostics by identifying disease signatures or indications.

Vahabi S et al., 2020 conducted this descriptive-analytical cross-sectional research to associate concentration of Interleukin-17 (IL-17) and Interleukin-18 (IL-18) in saliva in patients with CP and healthy participants. 20 subjects with healthy gingival tissues along with twenty with chronic periodontitis gave salivary samples which were unstimulated in addition to full-mouth clinical recordings of the periodontium. Salivary IL17 and IL18 were determined using ELISA. They discovered that patients with chronic periodontitis had greater mean salivary IL-18 level (143.10 pg/mL) than healthy controls (78.33 pg/mL) compared to healthy controls. Patients with CP and healthy controls had mean IL-17 salivary concentrations of 3.51 and 4.57 pg/mL, subsequently, with minimum meaningful variation amongst the two groups. Given constraints of current investigation, it is possible to hypothesise that higher salivary IL-18 measures within people with chronic periodontitis may serve equally a biomarker for periodontal tissue degeneration.

Betsy J et al., 2019 study's goal was to evaluate the diagnostic efficacy of a degradation fraction of type I collagen's C-terminal telopeptide (CTX), osteocalcin (OC), which contains deoxypyridinoline. and Osteonectin (ON) in the detection of individuals who have alveolar bone loss (BL) caused by periodontitis. 90 patients healthy, periodontitis with DM-2 and periodontitis without Type 2 DM) had their salivary levels of CTX, OC, and ON assessed. These patients' bleeding upon probing, probing pocket depth, and bleeding level (BL) was noted. Salivary OC, ON & CTX concentrations were demonstrated to be improved in patients with periodontal disease when evaluated to controls. These biomarkers and periodontal parameters were shown to be significantly correlated with one another. Regarding bone loss and probing pocket, CTX, ON & OC can distinguish between healthy individuals along with patients suffering from periodontitis.

Nisha KJ et al., 2019 undertook this study to better understand salivary miRNAs and recognise the effective salivary micro-RNA biomarker for treating CP. This research, two unstimulated samples of saliva from subject with generalised chronic periodontitis and a healthy control were collected using the passive drool method. The probable use of next-generation sequencing (NGS) for miRNA profiling was also examined. Saliva samples from 16 patients with chronic periodontitis as well as periodontally healthy controls were used to validate the most substantially expressed known miRNA in periodontal disease adopting quantitative real-time PCR. In comparison to healthy controls, NGS research

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found that 40 known miRNAs were elevated and 40 were downregulated in chronic periodontitis. MiR-143-3p was the utmost substantially articulated micro-RNA in periodontitis. The test group's expression of miR-143-3p was significantly upregulated as compared to the controls, according to validation using q RT-PCR. The study suggested a useful method for identifying new biomarkers in periodontal diagnosis is the use of NGS for micro-RNA expression profiling. The study's findings also suggest that miR143-3p may be useful as an innovative salivary biomarker for chronic periodontitis.

Schmalz G et al., 2019 conducted a cross-sectional investigation, where healthy individuals were examined for relationships among salivary active matrix-metalloproteinase 8 (aMMP-8) and rigorousness of periodontitis, possible periodontal microorganisms, and blood parameters. As a result, 188 subjects were investigated. Based on clinical attachment level and periodontal probing depth, the severity of the disease was determined. A commercially available and validated test system was used to conduct both aMMP-8 and microbiological analyses. The prevalence of Tannerella forsythia, Porphyromonas gingivalis, Parvimonas micra, Prevotella intermedia, Eubacterium nodatum and Camphylobacter rectus were significantly correlated with the aMMP-8 results. However, there were no connections between aMMP-8 and the investigated blood components. As a result, it was determined that the chairside, saliva-based aMMP-8 test relates to the degree of periodontitis and the presence of various periodontopathogens then to routine blood count results in systemically healthy individuals.

Isola, G., et al, 2019 investigated effects of periodontitis, coronary heart disease, and a combination of the two disorders (periodontitis + CHD) on salivary and serum levels of Malondialdehyde. MAA has been shown to play a critical part in endothelial functioning that leads to periodontitis and the development of coronary heart disease in a lipid pathway. Periodontal parameters were noted, serum and salivary samples were taken from thirty-two healthy people, thirty-four periodontitis patients, thirty-three CHD patients, and thirty-four periodontitis and CHD patients. The examination included the lipid profile, as well as malondialdehyde and C-reactive protein levels. Patients in the periodontitis and periodontitis + CHD groups had greater median salivary and serum MAA concentrations than individuals in the CHD and control groups. Periodontitis, CHD, and CRP were all substantially linked with MAA in univariate models. Only CRP persisted a relevant predictor of serum and salivary MAA levels in the multivariate model. When compared to controls and CHD patients, patients with periodontitis and periodontitis + CHD had greater levels of MAA in serum and saliva. CRP levels in the saliva and serum have been demonstrated to be a strong predictor of higher MAA levels.

Yoshida, R. A. et al., 2019 in their clinical experiment purposed to see how periodontal therapy affected cytokine levels in saliva and clinical characteristics in people with cerebral spastic cerebral palsy. Thirty-eight participants were included and randomised to groups G2 or G1 based on gingival index scores ranging from 0 to 1. Periodontal therapy included instructions in proper oral hygiene maintenance, traditional mechanical treatment, and an adjunct of 0.12% chlorhexidine. At the baseline and 15-day follow-up visits, clinical parameters and saliva samples were obtained. Periodontal screening and recording, as well as bleeding on probing, were determined. A cytometric bead array was used to assess the osmolality and flow rate of saliva and levels of cytokines interleukins 1,6,8 and 10, TNF- α and IL-12p70 in non-stimulated saliva samples. Periodontal clinical indicators differed considerably across groups at the beginning of the study and follow-up. At both timepoints, flow rate of the saliva and osmolality were comparable in both groups. TNF- α and I L-1 levels, on the other hand, were greater in G1 than in G2. Mechanical therapy improved clinical indicators in both G1 and G2. Additionally, both groups saw a substantial drop in salivary IL-1 and IL-8 levels following mechanical therapy.

Yarkac, F. U. et al., 2018 study goal was to see how nonsurgical periodontal care affected the stress-linked hormones and cytokine levels in GCF and saliva in pregnant & nonpregnant women with gingivitis. The research only included subjects who had. Clinical data, as well as crevicular fluid and saliva samples, were obtained at the beginning and end of periodontal management. To quantify the interleukins level and chromogranin A (CgA) hormone levels ELISA was used. Periodontal therapy reduced gingival inflammation in both groups and lessened the amount of IL-1 in GCF in the non-pregnant group; nevertheless, significant change

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was not seen in the test group. CgA hormone concentrations were lowered in both groups following periodontal treatment (p0.05). However, there was no change between the groups in GCF IL-10 levels, salivary CgA concentration, or perceived stress scale (PSS). Periodontal treatment considerably improved periodontal condition and stress level within the constraints of this research. Furthermore, the intensity of inflammation in gingival tissues in pregnancy was linked to stress.

4. Challenges and potential solutions

Before the goal of salivary diagnostics may be achieved it's necessary that a panel of specific biomarkers for periodontal health and disease are identified and validated and highly sensitive but easily available and inexpensive technologies are developed which may help distinguish between the biomarkers.

During the past, an array of salivary biomarkers has been used to differentiate amongst healthy individuals and patients with gingival inflammation and periodontitis. Nevertheless, the results have been inconsistent. Periodontal diseases go through various stages, from gingival inflammation to destruction of connective tissue, alveolar bone at advanced phases of periodontal destruction. As the biomarkers change with changing phases of periodontal disease, a robust panel of biomarkers need to be classified to help effectively classify sites which are in active phase of disease, stable periodontium, and therapeutic responses.

Another common problem is the loss of participants to follow up (Yoshida et al., 2019) as periodontitis is generally a chronic phenomenon, with an ideal step wise management, and for better correlations of salivary biomarkers with disease or therapy, a long-term follow is required.

Also, the indicators present within saliva are too low to be reliably and reproducibly detected, which is the most frequently cited objection to utilising saliva as a diagnostic fluid. Thus, there is a need to develop technologies with greater sensitivity and specificity to detect biomarkers associated with various stages of periodontal disease.

Salivary biomarkers have the potential to be used to identify periodontal status in special groups like pregnant females, smokers, patients with diabetes, heart diseases, mucocutaneous disorders like psoriasis. However, there is a requirement to develop trustworthy point of care (POC) technology devices based on saliva with enhanced sensitivity and specificity to detect biomarkers, that may be incorporated in chair-side diagnostics, risk assessment as well as self-screening. This is due to the emergence of salivary diagnostics and biotechnology as well as the enhancement of microchips and microfluidic proposals for salivary components.

Since, saliva is a biofluid with contribution from crevicular fluid, serum, oral cavity and reflects a whole mouth analysis sample. The components of saliva are thought to be developing diagnostic biomarkers for periodontal disease. Numerous salivary biomarkers ought to be suggested as potential nominees for the periodontitis diagnosis. Saliva has been found to contain periodontopathic bacteria, inflammatory mediators, and other periodontal disease contributing components. However, he long-term process of identifying validated salivary biomarkers for diagnosing and treating periodontitis is continuing (Hartenbach et al., 2020).

On evaluation of the diagnostic efficacy of a panel of salivary biomarkers representing microbes (Porphyromonas gingivalis), inflammation (inflammatory marker Interleukin -1 beta), host inflammatory response (host-derived proteolytic enzyme (matrix metalloproteinase (MMP)-8), tissue, and bone destruction marker (pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP)) in healthy, gingivitis, periodontitis subjects it was revealed that a combination of these markers may be used for discriminating periodontal health from subjects with gingivitis and periodontitis (Zhang et al., 2021). Utilization of the elevated salivary concentration of Interleukin -18 (Vahabi et al., 2020), changes in the levels of salivary matrix metalloproteinases (MMPs) post periodontal therapy (Kim, 2022) alteration of myeloid-related markers in subjects with periodontitis and the modification in their salivary level by periodontal treatment (Lira-Junior et al., 2021), application of salivary bone turnover markers to distinguish periodontal health from periodontal destruction (Betsy et al., 2019) has been studied to help validate a panel of biomarkers for periodontal disease. Numerous interleukins, Interferon gamma, TNF alpha, macrophage colony-stimulating factor, macrophage-activating factor,

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macrophage inflammatory protein, MMPs (Chen et al., 2021, Görgülü, 2022) have been studies. The studies have used the biomarkers in saliva to assess the response of therapy (Alkimavičienė et al, 2023, Görgülü, 2022).

When the impact of smoking on periodontium and the biomarkers was studied, (Varghese et al, 2020, Joseph et al., 2020) 8-hydroxyguanosine and markers of alveolar bone destruction demonstrated positive correlation. Salivary biomarkers have been successfully applied in the assessment of periodontal status in pregnant women (Yarkac et al., 2018), diabetic individuals (Rabelo et al., 2021), cerebral palsy (Yoshida et al., 2019, coronary heart disease (Isola et al., 2019), rheumatoid arthritis (Tar et al, 2021) and psoriasis (Ucan Yarkac et al., 2020) in various research studies.

However continuous, multi-centric, longitudinal, unbiased research is necessary for definitive identification and validation of various salivary markers.

The lower quantities of the biomarkers in the saliva have been addressed by the development of increasingly sensitive detection techniques. The amalgamation of promising biotechnologies and salivary diagnostics has the ability of to act as chairside tools for dentists. Currently no FDA approved salivary diagnostic assessments exists for estimating risk of periodontal disease. However, researchers have found promising results on using salivary lateral flow test (LFT) MM)-9 point-of-care kit (Kim et al., 2020), active matrix-metalloproteinase 8 (aMMP-8) chairside test kit (Schmalz et al.,) and a semiquantitative urinary strip test for evaluation of salivary markers of periodontal inflammation in saliva (Ramenzoni et al., 2021).

Thus, with the advent of new and improved biotechnologies and development of disease and therapy specific salivary biomarker panel the development of reasonable, feasible, and quick and efficient chairside diagnostic kit will be a reality in near future.

5. Conclusion

Saliva is a valuable diagnostic fluid due to its bioavailability and non-invasive accessibility. The discovery of biomarkers is a viable strategy for assessing periodontal problems. The use of both combinations and individual salivary biomarkers in the detection of periodontal disease may be beneficial. However, more extensive, and systematic research is required to verify these biomarkers.

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